**REMARKS/ARGUMENTS**

This is a response to the final Office Action dated August 13, 2004. A Notice of Appeal was filed February 11, 2005. The Appeal Brief was due on April 11, 2005. Applicants are submitting a Request for Continued Examination (RCE) under 37 CFR § 114 with this amendment and new argument as a submission. A five (5) month extension of time, also requested with this RCE, extends the time for filing the RCE to September 11, 2005. Accordingly, this response is timely filed.

In view of the following remarks and amendments, Applicants respectfully submit that all pending claims are now in condition for allowance.

Claims 96-97 and 99-107 are currently pending in the present application. Claims 1-94 and 98 have been cancelled and claims 95-107 have been previously added. Claims 96-97 and 99-107 are rejected under 35 USC §112, first paragraph. Claims 96-97 and 99-107 are rejected under 35 USC §103(a). Claims 96 and 97 are independent claims. Claims 99-107 are multiple dependent claims dependent upon Claims 96 and 97. By this amendment Claims 96, 97, 101, 102 and 106 have been amended, thus overcoming the rejections.

Applicants are now represented by attorneys from the Navy after being previously represented by the law firm of Hale & Dorr. Applicants thank the Examiner for the helpful phone conversations on August 25, 2005 and August 31, 2005 regarding the status of this application. Based on those discussions, Applicants are concerned that the file wrapper has not sufficiently developed the legal issues regarding the application of Levine et al. which is an evidentiary reference in the 35 USC 103(a) rejection and is discussed below. Applicants have also discovered that the previously filed 132

declaration should have indicated that the methods as well as the product of the instant claims was the sole invention of Applicant, Carl June. Applicants also believe that June et al. might be overcome by editing the previously submitted 132 declaration to that effect.

**1. 35 U.S.C. §112, first paragraph**

Claims 96-97 and 99-107 are rejected under 35 USC §112, first paragraph because the specification, while enabling for "antigen binding fragments that bind either CD3 or CD28, is not enabling for the recitation, "fragment thereof" of an anti-CD-3 or anti-CD 28 antibody.

Claims 96-97 and 99-107 are also rejected under 35 USC §112, first paragraph because the specification while enabling for "measuring CCR5 mRNA or protein," is not enabling for "measuring CCR5 expression by any other parameter."

**Response**

By this Amendment, Claims 96-97, 101-102 and 106 have been amended, thus overcoming the rejections. Applicants respectfully request the 35 USC §112, first paragraph rejections be reconsidered and withdrawn.

**2. 35 U.S.C. §103(a)**

Claims 96-97 and 99-107 are rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over June et al. (U.S. Pat. 6,352,694) in view of Levine et al. (Science 272:

1939-1942, 1996); Chang et al. (U.S. Pat. 6,129,916) and newly added Kwon et al. (U.S. Pat. 6,569,997 vice 5,569,997) and Alloway et al. (U.S. 2004/0086528 A1).

**Response**

By this Amendment, Independent Claims 96 and 97 and dependent claims 99-107 are amended to more clearly indicate what applicants Applicants have invented. June et al. (U.S. Pat. 6,352,694), Levine et al. (Science 272: 1939-1942, 1996); Chang et al. (U.S. Pat. 6,129,916) and newly add Kwon et al. (U.S. Pat. 6,569,997) and Alloway et al. (U.S. 2004/0086528 A1) fails to establish a prima facie case of obviousness under 35 USC 103(a) because the references as a whole do not teach each and every element of amended Independent Claims 96 and 97. The rejection by Levine et al. under 35 USC 102(a) was previously overcome by a 1.32 declaration. Thus, Independent Claims 96 and 97 are allowable as well as dependent claims 99-107.

Amended Independent Claim 96 is drawn to an *ex vivo* method for down-regulating CCR5 expression in a T cell comprising contacting the T cell with a single bead comprising both an anti-CD28 antibody or antigen binding fragments and an anti-CD3 antibody or antigen binding fragments immobilized on said bead; and measuring the level of CCR5 RNA or protein expression in said contacted T cell. Independent Claim 97 is drawn to a method for down-regulating CCR5 RNA protein expression in a T cell, comprising contacting the T cell *in vivo* with a single bead comprising both an anti-CD28 antibody or antigen binding fragments and an anti-CD3 antibody or antigen binding fragments immobilized on the same bead; and measuring the level of CCR5 RNA protein

expression in said contacted T cell. Claim 99-107 are multiple dependent claims of Claims 96 and 97.

The Office Action alleges that the combination of the primary references, June, Chang, and newly added Kwon and Allaway teach the beneficial effects of contacting T cells with anti-CD3 and anti-CD28 antibodies to increase HIV resistance and that the beneficial effect was a result of down regulation of CCR5. Thus one of skill in the art would have been motivated to combine the teachings of the references in order to induce an HIV resistant state and to monitor the expression of CCR5 expression as a result of the combining the effect of anti-CD3 and anti-CD28 antibodies on T cell populations on HIV expression. It is also alleged that the prior art teaches the co-immobilization of anti-CD3 and anti-CD28 on the same bead as a means of stimulating T cells. Levine et al. is cited to establish evidence of inherency of the resistance of T cells to infection with the M-tropic (CCR5 dependent) HIV-1 strain following contact of T cells with a solid phase surface that is a bead comprising an anti-CD3 and anti-CD28 antibody in vitro. Levine is also alleged to show the inherency of down-regulation of CCR5 (as evidenced by the resistance to infection by M-tropic HIV strains.) See Office Action of Nov.5, 2003.

Independent claims 96 and 97 drawn to methods of down-regulating CCR5 in a T cell have been amended to clearly state that anti-CD3 and anti-CD28 antibodies are both immobilized on the same bead and that said bead is used to contact a T-cell to down-regulate HIV-1 cofactor, specifically, CCR5 expression. Applicants further contend that June et al and Levine et al. have been overcome by evidence that the subject matter contained in each is, in fact, Applicant's own work, thus obviating the rejection.

Remaining references, Chang, Kwon and Allaway fail to teach the use of anti-CD3 and anti-CD28 immobilized on the same bead to contact T cells to down-regulate CCR5.

Applicants further contend that evidence of inherency of down-regulation of CCR5 alleged to be contained in Levine et al. is speculative and would not be recognized by one of skill in the art and is not supported by the evidence of record as will be shown below.

*June et al as prior art reference*

June et al. ('694 patent), teaches and claims a method for inducing an expansion of T cells for use as a therapeutic approach in immuno-deficient patients. The method comprises activating the population of T cells by contacting the T cells in vitro with an anti-CD3 antibody that is immobilized on a solid surface and stimulating an accessory molecule on the surface of the T cells *in vitro* with an anti-CD28 antibody, wherein the anti-CD28 antibody is immobilized on the same solid surface as the anti-CD3 antibody, the activating and stimulating steps thereby inducing proliferation of the T cells to sufficient numbers for use in therapy. June et al. teaches that a one of several solid surfaces that can be used for inducing proliferation of T cells, in addition to tissue culture dish, are microbeads. See claims 1 through 6 of June '694 patent. The current invention teaches a method for the induction of HIV resistance by the down regulation of CCR5 using anti-CD28 and anti-CD3 antibody on the surface of a bead.

Although June '694 teaches the use of multiple solid surfaces for immobilizing stimulating antibody, it was only after further studies that it became clear that only antibody attached to a bead but not antibody attached to other surfaces are able to induce

resistance to HIV infection. This was also reported subsequently by Creson, et al. (J. Virol. Vol 73 (11): 9337-9347). Therefore, one skilled in the art, at the time the application was filed, would not be able to apply that taught by June '694 for the down-regulation of CCR5. The current invention teaches a method for the induction of HIV resistance by the down regulation of CCR5 using anti-CD28 and anti-CD3 antibody on the surface of a bead. Therefore, June '694 fails to teach each and every claim of the current invention.

Moreover, June et al. fails to teach the use of anti-CD3 and anti-CD28 immobilized on the same bead to induce HIV resistance and to monitor anti-CD3/anti-CD28 stimulated T cells by monitoring CCR5 expression. The current invention (see Example 4) teaches the critical element of anti-CD3 and anti-CD28 co-immobilized on the same bead in order to induce HIV resistance.

Additionally, the claims have been rejected under 35 U.S.C. § 102(e) based on the June '694 patent. A 132 declaration dated June 4, 2003 and filed in the response dated July 17, 2003, indicating the solid phase surface immobilized with anti-CD3 and anti-CD28 antibodies and the magnetic immunobead with anti-CD3 and anti-CD28 antibodies disclosed in the June '694 patent was his own work and was not a work by others as to the instant application. However, the Nov. 5, 2003 Office Action found the 132 declaration to be insufficient to overcome the '694 June reference because the declaration only addresses the product used in the method of claims 1, 55, 87-90 and 92-94.

The June '694 patent and the current applicant application both teach methods for the stimulation of T cells using anti-CD3 and anti-CD28 on beads. The July 17, 2003 declaration addresses the fact that Carl June is the inventor of a "solid phase surface

immobilized with anti-CD3 and anti-CD28 antibodies that was disclosed but not claimed in U.S. Patent No. 6,352,694 to down-regulate HIV-fusion cofactors and CCR5." Because the declaration wording indicates the application of the product to the down-regulation of HIV-fusion cofactors and CCR5 the Applicants contend that the work of Carl June also includes the methods as well as the products used in the claimed methods of claims and thus is sufficient to overcome the'694 June reference. See MPEP 2136.05.

Therefore, Applicant's contend that the 35 U.S.C § 102(e) rejection based on June et al. (i.e. June '694 patent) has been overcome and should be removed.

*Levine, et al is not available as evidence of inherency.*

In the Office Action of November 5, 2003, the 35 USC 102(a) rejection based upon Levine was obviated against then pending claims 1, 55, 87-90, 92 and 94. However, Levine et al. is now being cited to establish evidence of inherency, in light of Chang, et al., of the resistance of T cells to infection with the M-tropic (CCR5 dependent) HIV-1 strain following contact of T cells with a solid phase surface that is a bead comprising an anti-CD3 and anti-CD28 antibody *in vitro*. Levine is also alleged to show the inherency of down-regulation of CCR5 (as evidenced by the resistance to infection by M-tropic HIV strains.) See Office Action of Nov.5, 2003.

In the June 22, 2003 Office Action, the rejection states that Levine et al. teaches a method of contacting T cells with a solid phase surface comprising an anti-CD3 and anti-CD28 antibody. Levine, et al teaches the culturing of lymphocytes from patients with HIV-1 infection in the presence of beads coated with anti-CD3 and anti-CD28 antibody. However, in order for evidence to be recognized as inherent, it must be "recognized by

persons of ordinary skill." MPEP 2131.01(III). However, as later taught by Creson, et al. (J. Virol., vol 73 (11): 9337-9347), it was not fully appreciated to one of skill in the art that beads, but not tissue culture plates, could be used to induce HIV resistance. Therefore, Levine cannot be used as evidence of the inherency of using that taught by Chang, et al in the induction of HIV resistance or for the reduction in CCR5. Furthermore, Levine, et al does not teach the importance of anti-CD28 and anti-CD3 antibodies being immobilized on the same bead. Therefore, Applicants contend this reference is ineffective as evidence that downregulation of CCR5 would be inherent.

*Chang et al is not available as prior art under 35 U.SC. § 103.*

The Office Action of January 22, 2003 alleges that Chang teaches and claims a method of comprising contacting T cells with a microbead coupled with a plurality of binding molecules specific for an antigen on a human T cell, wherein the molecules are an antibody to CD3 and an antibody to CD28. See column 11-12 and claims 1-2. In order for a reference to be an effective in a rejection based on 35 U.SC. § 102(e) each and every element must be taught. Chang, et al, however, does not teach the critical elements that only beads can be utilized to immobilize the stimulatory antibody and that both anti-CD3 and anti-CD28 being immobilized on the same bead.

There is no suggestion in the teaching of Chang that use of anti-CD3 and anti-CD28 attached to solid surfaces will lead to anything but to activation and T cell expansion. It was not appreciated, at the time of filing, that only beads but not other solid surfaces could be used in to immobilize the stimulatory antibody. This fact was subsequently reported by Creson, et al (J. Virol., vol 73 (11): 9337-9347). Therefore, one

skilled in the art would be unable to recognize the likelihood of obtaining HIV resistance using antibody coupled beads, since previous references, including Chang, et al, had observed only proliferation of T cells. HIV resistance would not have been possible at the time of filing without further experimentation. The references Kwon, Levine and/or June '694, if combined with Chang, do not supply missing information to enable reproduction of the inventive method taught in the current application. Therefore, this reference is not effective as a reference under 35 U.S.C. §103 and the Applicants respectfully request that this rejection be withdrawn.

*Kwon et al is not available as prior art under 35 U.SC. § 103.*

Kwon teaches that activation of CD4+ T cells from HIV-1 infected donors with immobilized anti-CD3 and anti-CD28 antibody induces a virus-resistant state. This effect was specific for macrophage-trophic HIV-1 and appears to be the result of down-regulation of CCR5, the fusion co-factor. See Kwon at col. 28, lines 9-16. The reference however, does not teach nor suggest the critical element taught in the claimed method that only stimulation of cells using anti-CD3 and anti-CD28 on beads, but not antibody immobilized to other solid surfaces are effective at inducing HIV resistance. Kwon also does not teach that the beads must contain anti-CD3 and anti-CD28 co-immobilized on the same bead. These critical elements were not appreciated at the time filing. Although one of ordinary would possibly appreciate, based on the teaching of Kwon, that immobilized anti-CD3 and anti-CD28 would lead to a virus-resistant state. However, one of ordinary skill in the art would not have appreciated the critical elements, as taught by the claimed method in the current application, that only anti-CD3 and anti-CD28 on

beads and co-immobilized on the same bead is required for reproducible induction of virus-resistance. Only subsequent to the filing of the current application was the importance of beads in inducing virus-resistance taught. Creson, et al (J. Virol., vol 73 (11): 9337-9347). Combining Kwon with other alleged prior art references, including June '694, Chang, Levine or Allaway do not supply the missing information to enable one of ordinary skill in the art to reproducibly induce HIV resistance without further experimentation. Therefore, this reference is ineffective as a prior art for a rejection under 35 U.S.C. §103.

*Alloway et al is not available as prior art under 35 U.SC. § 103.*

Allaway, et al teaches methods to measure CCR5 availability on the surface of T cells and whether it is sufficient for permitting HIV entry and infection. However, Allaway et al fails to teach a method of monitoring CCR5 expression in T cells following induction of HIV resistance with anti-CD3 and anti-CD28 co-immobilized on a bead as taught in the claimed method. There is no motivation to combine the teachings of Allaway, et al. with Chang, Kwon, June or Levine in order to ultimately teach all the claim limitations of the current invention, specifically a method of inducing an HIV resistant state using anti-CD3 and anti-CD28 co-immobilized onto a microbead and monitoring the results of this stimulation by measuring CCR5. Therefore, Allaway is ineffective as a prior art for a rejection under 35 U.S.C. §103.

*Summary*

Applicants contend that the '694 June patent and Levine have been overcome. The remaining combination of *Chang*, Kwon and Allaway, singly or in combination, in view of Levine or with June '694 fails to teach the use of anti-CD3 and anti-CD28 co-immobilized on a microbead, as taught in the claimed method, in order to induce an HIV-resistant state. Furthermore, the references, alone or in combination do not teach the monitoring of HIV resistance, following stimulation using the claimed method by measuring CCR5.

None of the references, singly or in combination, teach the critical nature of using beads verses other solid surfaces. Also, none of the references, singly or in combination teach the critical element taught in the claimed method of co-immobilizing both anti-CD3 and anti-CD28 on the same bead. Rather, the references merely provided an impetus to further explore how to obtain efficient induction of HIV resistance. Creson, et al. (J. Virol., vol 73 (11): 9337-9347) provides evidence that one of ordinary skill in the art would not have appreciated the difference in HIV resistance between a method using anti-CD28 immobilized on a bead verses other methods such as those where anti-CD28 is immobilized to other solid surfaces. This knowledge was only obtained after significant experimentation and study.

In view of the amendment to the claims and the above stated arguments, Applicants contend the case is now in condition for allowance. An early and favorable reply is requested.

Respectfully submitted,

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